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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : **A61K 31/00, 31/40, 31/445**

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(43) International Publication Date: 23 July 1998 (23.07.98)

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(30) Priority Data:
9700899.9 17 January 1997 (17.01.97) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: KENNETT, Guy, Anthony [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: WATERS, David, Martin; SmithKline Beecham plc, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

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With international search report.

(88) Date of publication of the international search report:
17 September 1998 (17.09.98)

(54) Title: USE OF 5-HT_{2B} AGONISTS OR POTENTIATORS IN CNS DISORDERS

(57) Abstract

The present invention discloses the use of 5-HT_{2B} agonists or positive allosteric modulators (enhancers) such as paroxetine or BW-723C86 in the treatment of various CNS, affective, behavioral, migraine or feeding disorders, and in particular in depression.

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INTERNATIONAL SEARCH REPORT

Inter. .onal Application No
PCT/EP 98/00380

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/40 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	KENNETT ET AL: "Effects o the 5-HT2B receptor agonist, BW 723C86, on three rat models of anxiety" BR. J. PHARMACOL., vol. 117, no. 7, April 1996, pages 1443-1448, XP002069364 cited in the application see the whole document ---	1,2,5
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 1998	15. 07. 1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

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INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/00380

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ɔnal Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9425012 A	10-11-1994	AU 6569794 A	21-11-1994
		ZA 9402809 A	23-10-1995
WO 9629074 A	26-09-1996	AU 5528996 A	08-10-1996

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Name and mailing address of the ISA	Authorized officer
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Published
Without international search report and to be republished upon receipt of that report.

(54) Title: NOVEL TREATMENT

(57) Abstract

The use of a 5-HT_{2B} agonist for the treatment of depression and other CNS disease conditions.

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NOVEL TREATMENT

The present invention relates to a novel treatment of CNS disorders, in particular the treatment of depression.

Compounds which act as $5HT_{2B}$ antagonists are known in the art, e.g. WO 95/01976 .

It is now believed that treatments selectively increasing 5-HT_{2B} receptor function, such as administration of 5-HT_{2B} receptor agonists or positive allosteric modulators of the 5-HT_{2B} receptor (i.e. potentiators acting at modulating sites), would mimick the mode of action of selective serotonin (5-HT) reuptake inhibitors (SSRIs) and be an effective treatment for depression, Panic disorder, obsessive compulsive disorder, migraine, bulimia, premenstrual tension, social phobia, addictions to drugs of abuse, behavioural disturbances associated with dementia, atypical depression, chronic fatigue syndrome and the negative symptoms of schizophrenia.

In a first aspect the present invention therefore provides the use of a $5HT_{2B}$ agonist for the treatment of the above disorders, in particular depression.

Chronic, but not acute administration of SSRIs, such as paroxetine, are widely reported to be clinically effective antidepressants (Boyer and Feighner, 1992; Lane et al., 1995). Anxiety is a significant component of depression with as many as two thirds of patients with depressive disorders also experiencing anxiety symptoms (Liebowitz et al., 1993). Epidemiological studies suggest that the co-morbidity of anxiety and depressive disorders is associated with increased severity and chronicity of the condition (Angst and Dohla-Mikola, 1985; Stravrakaki and Vargo, 1986), a reduced responsiveness to therapy and poorer outcome (Murphy et al., 1990). Although benzodiazepine anxiolytics are not effective in the treatment of depression (Widlocher et al., 1983), it is well documented that the SSRIs and other antidepressants are equally effective in treating both the anxiety and depressive symptomologies associated with depressive illness (Nutt et al., 1995; Sheehan et al., 1992; Lane et al., 1995). It is also apparent that the onset of therapeutic efficacy of the SSRIs in treating both anxiety and depressive symptomologies associated with depression follows the same time course, with a delayed onset (Nutt et al., 1995; Cohn and Wilcox, 1992). It is therefore likely that the mode of action of SSRIs in the treatment of both symptom groups is the same.

The precise mode of action of SSRIs, however, is uncertain. Whilst it is clear that they prevent the neuronal reuptake of released 5-hydroxytryptamine (5-HT) and hence might be expected to potentiate the actions of this neurotransmitter, studies have concluded that, acutely, SSRIs only modestly increase extraneuronal 5-HT levels at nerve terminals (Bel and Artigas, 1992; Invernizzi et al., 1994). In contrast, chronic administration of SSRIs may lead to more substantial increases of extraneuronal 5-HT at 5-HT nerve terminals (Bel and Artigas, 1993; Invernizzi et al., 1994). The difference between the effects of acute and chronic SSRI administration is presumed to be due to the onset of adaptive mechanisms, one of which may be the desensitization of 5-HT cell body autoreceptors (Jones 1994). Thus, the antidepressant effects of chronic SSRI administration are thought to be mediated through enhanced extraneuronal 5-HT levels. If this hypothesis is correct, then the therapeutic effects of SSRIs would be expected to be mediated by the activation of postsynaptic 5-HT receptors. The identification of the receptor, or receptors, involved is currently unknown and is complicated by the complexity of 5-HT receptor pharmacology. To date, at least 14 5-HT receptor subtypes have been recognised. These have been classified on the basis of structural, pharmacological and functional similarities into subgroups termed 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_{5A}, 5-HT_{5B}, 5-HT_6 and 5-HT_7 (Hoyer et al., 1994).

Until recently, there have been no drugs which discriminated between the 5-HT_2 receptor subtypes. 6-Chloro-5-methyl-1-(5-quinolylcarbamoyl) indoline (Compound 1) (Example 24 WO 95/01976) therefore represents a compound of some interest. Compound 1 was found to potently antagonise 5-HT-induced contractions of the rat stomach fundus (pA_2 9.8, table 1, example 1), a model of 5-HT_{2B} receptor function (Baxter et al., 1994, Kursar et al., 1992; Foquet et al., 1992) and thus acts as a high affinity 5-HT_{2B} receptor antagonist. In receptor binding assays, the affinity (pK_i) of Compound 1 for the human cloned 5-HT_{2C} receptor was found to be 7.7 and was less for all the other binding sites at which it was tested including the 5-HT_{2A} site (table 1, example 2). Thus, Compound 1 appears to have at least 100 fold selectivity for the 5-HT_{2B} receptor. Compound 1 (0.1 and 0.3 mg/kg p.o. 1 h pre-test) antagonised the anxiolytic-like effect of the 5-HT_{2B} receptor agonist, BW 723C86 (1-[5-thienylmethoxy-1H-3-indolyl]propan-2-amine) in the social interaction test (data not shown) , a model of 5-HT_{2B} receptor function (Kennett et al., 1996, Duxon et al., 1997), thus demonstrating that the compound is bioavailable and brain penetrant.

The possibility that the therapeutic effects of paroxetine and thus other SSRIs is mediated by the stimulation of 5-HT_{2B} receptors has been investigated in a rat social interaction

and Vogel conflict tests. In the social interaction test (see example 3 for details), pairs of like-treated rats are placed in a brightly lit arena with which they are unfamiliar. The aversive nature of the conditions suppresses the amount of time the rats spend in social interaction. Anxiolytic treatments are expected to disinhibit behaviour and increase time spent in social interaction. The test has been validated pharmacologically, physiologically and behaviourally (File, 1984). In the Vogel conflict test (see example 3 for details), thirsty rats are trained to drink from a water spout. On the test day, drinking may result in the delivery of an electric shock through the drinking spout. This suppresses drinking behaviour which is also expected to be disinhibited by anxiolytic treatments (Vogel et al., 1971). In both of these procedures, chronic, but not acute, paroxetine was found to produce anxiolytic-like effects and an optimal dose or 3 mg/kg p.o. x 21 days, last dose 1 h pre-test was identified (for social interaction test data see Lightowler et al., 1994). The effect of 5-HT_{2B} receptor antagonists on these two psychotropic effects of chronic paroxetine were therefore tested.

In the rat social interaction test, chronic paroxetine increased time spent in social interaction (fig 1) without affecting locomotion (data not shown). Thus, the action of chronic paroxetine is consistent with the compound exerting anxiolytic-like properties in this test (File and Hyde, 1978; File, 1984). In the rat Vogel conflict test, chronic paroxetine increased the number of shocks accepted (table 2), demonstrating that chronic paroxetine has an anxiolytic-like profile in a second model of anxiety (Vogel et al., 1971). These effects of chronic paroxetine thus mirror the therapeutic efficacy of the drug in affective disorders, particularly as in both models acute paroxetine was found to be ineffective (Lightowler et al., 1994 and unpublished data).

The anxiolytic-like effects of chronic paroxetine in the rat social interaction test were antagonised by the selective 5-HT_{2B} receptor antagonist, Compound 1 (0.1 and 0.3 mg/kg p.o., fig 1), although at the doses used, Compound 1 did not alter the amount of time spent in social interaction when given alone. The action of the compound is therefore unlikely to be secondary to a non-selective effect in the test. Results in the rat Vogel test were similar. The selective 5-HT_{2B} receptor antagonist Compound 1 blocked the anxiolytic-like effect of chronic paroxetine, yet had no effect when given alone in the test (Table 2). The results therefore imply that the effects of chronic paroxetine in both tests is mediated through the activation of 5-HT_{2B} receptors. If so, then the anxiolytic effects of paroxetine in man are also likely to be 5-HT_{2B} receptor mediated. Since the antidepressant and anxiolytic actions of paroxetine and other SSRIs coincide in terms of dose regimen and onset of action (Nutt et al., 1995; Cohn and Wilcox, 1992), it is likely

that they are both mediated by the same mechanism as argued above in page 1, lines 20-37. Furthermore, if the present studies have indeed identified the mechanism of paroxetine and hence other SSRIs, it is likely to account for the efficacy of this class of compounds in other mental disorders such as obsessive compulsive disorder, migraine, bulimia, premenstrual dysphoria, social phobia, Panic disorder, addictions to drugs of abuse, behavioural disturbances associated with dementia, atypical depression, chronic fatigue syndrome and the negative symptoms of schizophrenia (Schneier et al., 1990; Boyer, 1992; Kennett, 1993; Lane, 1994).

It is therefore claimed that treatments which enhance 5-HT_{2B} receptor function such as 5-HT_{2B} receptor agonists or positive allosteric modulators of the 5-HT_{2B} receptor would mimic the mode of action of SSRIs and be an effective treatment for depression, obsessive compulsive disorder, Panic disorder, migraine, bulimia, premenstrual tension, social phobia, addictions to drugs of abuse, behavioural disturbances associated with dementia, atypical depression, chronic fatigue syndrome and the negative symptoms of schizophrenia.

Treatments which enhance 5-HT_{2B} receptor function such as 5-HT_{2B} agonists or positive allosteric modulators, are expected to be of use in the treatment of the CNS disorders mentioned above, in particular depression. In another aspect the invention provides the use of a 5-HT_{2B} agonist or a positive allosteric modulator or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of a $5HT_{2B}$ agonist or a positive allosteric modulator or a pharmaceutically acceptable salt or solvate thereof.

A pharmaceutical composition based on the invention may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants

and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.
The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following examples and data illustrate the invention.

Materials

Compound 1 refers to 6-chloro-5-methyl-1-(5-quinolylcarbamoyl) indoline which was synthesised according to the procedure of WO 95/01976 (Example 24).

For in vivo studies, paroxetine HCl and Compound 1 were given orally as suspensions after grinding (using a mortar and pestle) into a 1% methyl celluose solution in 0.9% NaCl containing a drop of BRIJ 35 (Sigma Chemical Co.). Injection volumes of 2 ml/kg were used in all treatments. In the social interaction test, drug and vehicle also contained 10 mg/ml $BaSO_4$ to mask the presence of drug and were independently coded prior to experiments to establish blind conditions. Oral dosing took place 1 h before testing.

Example 1: Rat Stomach fundus assay.

Rats stomach fundi were excised and set up as described by Baxter et al., (1994). Briefly, two strips of longitudinal muscle were obtained from each stomach fundus and following removal of the mucosa were suspended under an initial resting tension of 1 g in oxygenated (95% O_2/5% CO_2) Tyrodes solution at 37 ^{0}C. Experiments were conducted in the presence of indomethacin (3 μM), after tissues had been exposed to pargyline (100 μM for 15 min). Two concentration-effect curves to 5-HT were constructed from each strip in the absence and presence of Compound 1. Time control curves to 5-HT at a 1 h interval were carried out in the same way without adding Compound 1. The pA_2 of Compound 1 versus 5-HT in the rat stomach fundus was calculated using Schild regression analysis, plotting $\log_{10}$ molar antagonist concentration against $-\log_{10}$ of the concentration ratios (CR-1) determined in individual experiments as detailed in Baxter et al., (1994).

Example 2: Binding assays

In all assays (for details see below), Compound 1 was dissolved in polyethylene glycol:dimethyl sulphoxide (1:1) at 10 mM and diluted to 0.1mM using 5mM Tris buffer (pH 7.7 @ 25°C). Dissolution was assisted where necessary by addition of 0.02 ml 5 M HCl plus heating to 40°C and sonication for 10 minutes. Oxidation of 5HT was attenuated by the inclusion of 10mM ascorbate in the buffer. Serial dilutions of Compound 1 in the same buffer were carried out using either a TECAN 5052 or Biomek 2000 Workstation.

0.05 ml of diluted Compound 1 were mixed with 0.05 ml of radioligand, prepared in the incubation buffer and 0.4 ml of the homogenate of washed membranes, also in the working buffer. In dopamine bimding assays 0.1% (w/v) bovine serum albumen was included in the incubation buffer.

After incubation at 37°C, samples were filtered using either a TOMTEC harvester in Wallac Betaplate format or a Packard Filtermate in Packard TopCount format. Filters were washed with 4 x 1ml aliquots of ice-cold incubation buffer. Filters were dried and either impregnated with Meltilex solid scintillant (Betaplate) or 0.04ml of Microscint 20 (Packard) and counted for radioactivity.

Data from receptor binding studies were analysed using the four parameter-logistic function (Bowen and Jerman, 1995) to determine the IC_{50} (concentration of test compound that inhibits specific binding or maximal response to 5-HT by 50%) or EC_{50} (concentration producing 50% of maximal response). The IC_{50} was then corrected to inhibitory affinity constant (K_i) according to Cheng and Prussof (1973) and expressed as the negative $\log_{10} K_i$ (pK_i).

Summary of receptor binding assay conditions

Receptor	Host cell or tissue source	incubation buffer	protein (ug/ assay)	radio-ligand	radio-ligand (nM)	Specific Activity (Ci/mmol)	Non-Specific Definition	Kd (nM)	References
5-HT_{1A}	HEK293	2	50	[^{3}H]-8-OH- DPAT	1.0	120	Buspirone	1.0	g
5-HT_{1B}	C.H.O.	2	70	[^{3}H]-5-HT	4.0	86	5-HT	4.0	a,b
5-HT_{1D}	C.H.O.	2	150	[^{3}H]-5-HT	4.0	86	5-HT	4.0	a,b
5-HT_{1E}	C.H.O.	2	120	[^{3}H]-5-HT	4.0	86	5-HT	24.0	a,b
5-HT_{1F}	C.H.O.	2	140	[^{3}H]-5-HT	4.0	86	5-HT	24.0	a,b,c
5-HT_{2A}	HEK293	1	170	[^{3}H]-ketanserin	0.5	80	Mianserin	0.7	d
5-HT_{2C}	HEK293	1	130	[^{3}H]-mesulergine	0.6	81	Mianserin	0.58	d
5-HT_4	Piglet Hippocampus	5	10	[125]-SB 207710	0.02	2000	SB 204070A	1.0	i
5-HT_6	HeLa	4	40	[^{3}H]-LSD	2.0	83	methiothepin	3.1	m
5-HT_7	HEK293	2	250	[^{3}H]-5-CT	0.5	79	5-HT	0.5	k
$D_{2\,(long)}$	C.H.O.	3	220	[^{125}I]-iodosulpride	0.1	2000	YM-09151	1.3	l,f
D_3	C.H.O.	3	60	[^{125}I]-iodosulpride	0.1	2000	YM-09151	2.4	l,f
$Ad_{\alpha 1B}$	C.H.O.	1	120	[^{3}H]-prazosin	0.2	76	Phentolamine	0.58	h

Incubation buffers were; 1) 50mM Trizma (Sigma, UK) pH 7.7 @ 25°C. 2) 50mM Trizma (Sigma, UK) pH 7.7 @ 25°C, 5mM $MgCl_2$, 500nM Pargyline, 10mM Ascorbate. 3) 50mM Trizma (Sigma, UK) pH 7.7 @ 25°C, 120mM NaCl, 5mM KCl, 2mM $CaCl_2$, 1mM $MgCl_2$. 4) 20mM HEPES 10mM MgSO4. Method references were; a, Hamblin and Metcalf (1991); b, Heuring and Peroutka (1987); c, Adham et al., (1993); d, Wood et al., (1995); f, Sokoloff et al., (1992); g, Gozlan et al., 1983; h, Testa et al., (1993); i, Brown et al., (1993); k, To et al., (1995); l, Bowen et al., (1993); m, Monsma et al., (1992).

Example 3

Male Sprague Dawley (CD) rats (220-250 g) were housed in groups of six under a 12 h light/dark cycle (lights on 07.00 h) with free access to food (CRMX, special Diet Services) and water.

Social Interaction

Rats were orally dosed with paroxetine 3 mg/kg or vehicle daily for 21 days, last dose 1 h pre-test. They were housed singly in a room adjacent to the testing room on day 17. On day 21, they were dosed p.o. 1 h before the test with antagonists or vehicle with or without paroxetine in treatment and weight (± 5 g) matched pairs unfamiliar to each other and returned to their home cages. Rats were then placed in a white perspex test box (54 x 37 x 26 cm) for 15 min under bright white light (150 lux) in an adjacent darkened room containing a fan to generate white noise. Active social interaction (sniffing, following, grooming, biting, boxing and crawling over or under) was scored by a "blind" observer by remote video monitoring and a computerised score pad. At the end of each test the box was thoroughly wiped with moistened tissue paper (for details see Kennett et al., 1994).

Vogel conflict test

Rats were orally dosed with paroxetine 3 mg/kg p.o. or vehicle daily x 21 days, last dose 1 h pre-test. On day 19 they were water deprived for 20 h prior to being placed in a uniformly lit operant conditioning chamber (45 x 25 x 25 cm) with a well (2.5 x 2.5 x 2.5 cm) set into one side of the cage 4 cm from the floor into which a water bottle spout protruded. A photocell beam traversed the well at a point just above the water spout, such that any animal drinking from the spout would break the beam. Rats were allowed to explore the chamber freely and drink for 3 min, timed after 30 seconds of continuous

drinking had been recorded via the photocell and a linked computer. The rat was then returned to the home cage, allowed access to water for 4 h and then water deprived again for 20 h. After 19 h water deprivation, rats were orally dosed with antagonists or vehicle with or without paroxetine and 1 h later placed in the test chamber. After 30 seconds of continuous drinking, each subsequent 5 seconds of cumulative drinking was punished by an electric shock (0.25 mA for 0.2 seconds) delivered through the water bottle spout and the latency to drink and the number of shocks accepted over 3 min was recorded.

Table 1: receptor affinity profile of Compound 1

Receptor	pK_i (*pA_2)	Receptor	pK_i
5-HT_{2B}	9.8*	Dopamine D_2	5.6
5-HT_{2A}	6.8	Dopamine D_3	5.6
5-HT_{2C}	7.7		
5-HT_{1A}	6.3		
5-HT_{1B}	6.8		
5-HT_{1D}	6.8		
5-HT_{1E}	5.0		
5-HT_{1F}	5.1		
5-HT_4	5.5		
5-HT_6	6.0		
5-HT_7	5.8		

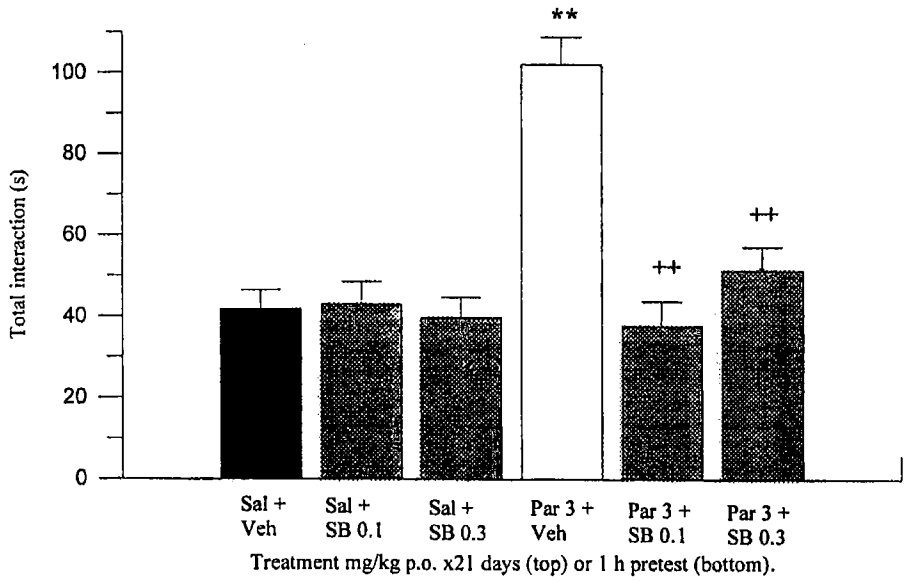
All points are means derived from at least 2 independent determinations, methodology as described in examples 1 and 2.

Table 2: Effect of acute Compound 1 and chronic paroxetine on the number of shocks accepted in a rat Vogel conflict test.

Pretreatment (p.o. daily x 21 days last dose 1 h pre-test)	Treatment (p.o. 1 h pre-test)	Number of shocks accepted
Vehicle	Vehicle	5.1 ± 0.7
Vehicle	Compound 1 3 mg/kg	6.7 ± 1.1
Paroxetine 3 mg/kg	Vehicle	10.0 ± 1.3**
Paroxetine 3 mg/kg	Compound 1 3 mg/kg	5.1 ± 0.7#

All data cited as means ± s.e.m., n=9-15. Significantly different from vehicle + vehicle treated rats ** $p<0.01$, from paroxetine + vehicle treated rats # $p<0.05$ by Newman-Keuls test and 2-way ANOVA. For method see example 3.

Fig 1: The effect of chronic paroxetine and acute Compound 1 on rat behaviour in a social interaction test.



'SB' refers to Compound 1.

All data cited as means ± s.e.m., n=10 per group. Significantly different from vehicle + vehicle treated group ** $p<0.01$, from paroxetine + vehicle treated group ## $p<0.01$, by Newman-Keuls test and 2-way ANOVA. for method see example 3.

Data analysis and statistics

Social interaction and Vogel conflict test data were analysed by 2-way ANOVA and Newman-Keuls post hoc multiple comparisons procedure. All data are cited as the mean ± s.e.m. unless otherwise indicated.

References:

Adham, N., Kao, H.T., Schechter, L.E., Bard, J., Olsen, M., Urquhart, D., Durkin, M., Hartig, P.R., Weinshank, R.L. and Branchek, A. (1993) Proc. Natl. Acad. Sci. USA., **90**, 408-412.

Angst, J., Dobler-Mikola, A., (1985). Eur. Arch. Psychiatr. Neurol. Sci., 235, 179-186.

Baxter, G.S., Murphy, O.E., Blackburn, T.P. (1994). Br. J. Pharmacol., 112, 323-331.

Bel, N., Artigas, F., (1992). Eur. J. Pharmacol., 229, 101-103.

Bel, N., Artigas, F., (1993). Synapse, 15, 243-245.

Bowen, W.P., Coldwell, M.C., Hicks, F.R., Riley, G.J. (1993). Br. J. Pharmacol., 108, 277P.

Bowen, W.P., Jerman, J.C., (1995). Trends in Pharmacol. Sci., 16, 413-417.

Boyer, W.F., (1992). Int. Clin. Psychopharmacol., 6 (Suppl 5), 5-12.

Boyer, W.F., Feighner, J.P. (1992). J. Clin Psychiat., 53 (Suppl), 3-6.

Brown, A.M., Young, T.J., Patch, T.L., Cheung, C.W., Kaumann, A.J., Gaster, L., King, F.D. (1993). Br. J. Pharmacol., 110, 10P.

Cheng, Y.C., Prussof, W.H., (1973). Biochem. Pharmacol., 92, 881-894.

Cohn, J.B., Wilcox, C.S., (1992). J. Clin. Psychiat., 53 (Suppl), 52-56.

Duxon, M.S., Kennett, G.A., Lightowler, S., Blackburn, T.P., Fone, K.C.F., (1997).. Neuropharmacology (in press).

File, S.E., (1984). Pol. J. Pharmacol., 36, 505-512.

File, S.E. and Hyde, J.R.G. (1978). Brit. J. Pharmacol., 62,19-24.

Foquet, M., Hoyer, D., Pardoe, L.A., Parekh, A., Kluxen, F.W., Kalkman, H.O., Stuhmer, W. and Lubbert, H. (1992). EMBO J. 11, 3481-3487.

Gozlan, H., El Mestikawy, S., Pichat, L., Glowinski, J., Hamon, M. (1983). Nature, 305, 140-142.

Hamblin, M.W. and Metcalf, M.A., (1991). Mol. Pharmacol., 40, 143-148.

Heuring, R.E. and Peroutka, S.J., (1987). J. Neurosci., 7, 894-903.

Hoyer, D. Clarke, D.E., Fozard, J.R., Hartig, P.R., Martin, G.R., Mylecharane, E.J., Saxena, P.R., and Humphrey, P.P.A. (1994). Pharmacol. Rev., 46, 157-203.

Invernizzi, R., Bramante, M., Samanin, R., (1994). Eur. J. Pharmacol., 260, 243-246.

Jones, B. J. (1994). Exp. Opin. Invest. Drugs, 3, 1033-1035.

Kennett, G.A. (1993). Curr. Opin. Invest. Drugs, 2, 317-362.

Kennett, G.A., Bright, F., Trail, B., Baxter, G.S. and Blackburn, T.P., (1996). Br. J. Pharmacol., 117, 1443-1448.

Kennett, G.A., Wood, M.D., Glen, A., Grewal, S., Forbes, I.T., Gadre, A., and Blackburn, T.P. (1994) Brit. J. Pharmacol, 111, 797-802.

Kursar, J.D., Nelson, D.L., Wainscott, D.B., Cohen, M.L. and Baez, M. (1992).. Mol. Pharmacol., 42, 549-557.

Lane, R., (1994). J. Serotonin Res., 1, 47-47-60.

Lane, R., Baldwin, D., Preskorn, S., (1995). J. Psychopharmacol., 9 (Suppl), 163-178.

Liebowitz, M.R. (1993). J. Clin. Psychiat., 54 (Suppl 2), 21-29.

Lightowler, S., Kennett, G.A., Williamson, J.R., Blackburn, T.P., Tulloch, I.F. (1994). Pharmacol. Biochem. Behav., 49, 281-285.

Monsma, F.J., Shen, Y., Ward, R.P., Hamblin, M.W. and Sibley, D.R., (1993) Mol. Pharmacol., 43, 320-327.

Murphy, J.M., (1990). Can. J. Psychiat., 35, 390-396.

Nutt, D. (1995). J. Psychopharmacol., (9 (Suppl), 185-189.

Schneier, F.R., Liebowitz, M.R., Davies, S.O., Fairbanks, J., Hollander, E., Campeas, R., Klein, D.F. (1990). J. Clin. Psychopharmacol., 10, 119-121.

Sheehan, D., Dunbar, G.C., Fuell, D.L. (1992) Psychopharacol. Bull., 28, 139-143.

Sokoloff P., Andrieux, M., Besancon, R., Pilon, C., Martres, M.-P., Giros, B. and Schwartz, J.C. (1992). Eur. J. Pharmacol., 225, 331-337.

Stavrakaki, C., Vargo, B. (1986). Br. J. Psychiat.,149, 7-16.

Testa, R., Guarneri,M., Ibba, M., Strada, G., Poggesi, E., Taddei, C., Simonazzi, I. and Leonardi, A. (1993). Eur. J. Pharmacol., 249, 307-315.

Trail, B., Ainsworth, K., Blackburn, T.P. and Kennett, G.A., (1995Br. J. Pharmacol., 116, 449P.

To, Z.P., Bonhaus, D.W., Eglen, R.M. and Jakeman, L.B. (1995). Brit. J. Pharmacol., 115, 107-116.

Vogel, J.R., Beer, B., Clody, D.E., (1971) Psychopharmacology, 21, 1-7.

Widlocher, D., Lecrubier, Y., Le Goc, Y. (1983). Br. J. Pharmacol., 15, 171S-179S.

Wood, M.D., Glen, A., Gager, T.L., Blackburn, T.P., Lee, J.A., Sutiphong, J.A., Kumar, C., Carey, J.E. and Robinson, J.H. (1995). Pharmacol. Commun., 5, 109-116.

CLAIMS:

1. The use of treatments enhancing 5-HT_{2B} receptor function such as a 5-HT_{2B} agonist or positive allosteric modulator for the treatment of depression, obsessive compulsive disorder, panic disorder, migraine, bulimia, premenstrual tension, social phobia, addictions to drugs of abuse, behavioural disturbances associated with dementia, atypical depression, chronic fatigue syndrome and/or the negative symptoms of schizophrenia.

2. The use of a 5-HT_{2B} agonist for the treatment of depression, obsessive compulsive disorder, panic disorder, migraine, bulimia, premenstrual tension, social phobia, addictions to drugs of abuse, behavioural disturbances associated with dementia, atypical depression, chronic fatigue syndrome and/or the negative symptoms of schizophrenia.

3. The use of a 5-HT_{2B} agonist or a positive allosteric modulator or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of depression.

4. A method of treating depression which comprises administering an effective amount to a patient in need of such treatment of a compound of a $5HT_{2B}$ agonist or a positive allosteric modulator or a pharmaceutically acceptable salt or solvate thereof.

5. A use according to any one of claims 1 to 3 in which the $5HT_{2B}$ agonist is 1-[5-thienylmethoxy-1H-3-indolyl]propan-2-amine.